

Effects of Inhaled Acid Aerosols on Lung Mechanics: An Analysis of Human Exposure Studies

by Mark J. Utell*

There exist significant gaps in our understanding of human health effects from inhalation of pollutants associated with acid precipitation. Controlled clinical studies examine effects of criteria pollutants almost exclusively by assessing changes in lung mechanics. One constituent of acid precipitation, sulfuric acid aerosols, has been shown to induce bronchoconstriction in exercising extrinsic asthmatics at near ambient levels. These asthmatics may be an order of magnitude more sensitive to sulfuric acid aerosols than normal adults. More recently, a second component nitrogen dioxide has been observed to provoke changes in lung mechanics at progressively lower concentrations. To date, virtually no data exist from clinical exposures to acidic aerosols for subjects with chronic obstructive pulmonary disease.

Introduction

There exist significant gaps in our knowledge of human health effects resulting from inhalation of pollutants associated with acid precipitation. Although such precipitation consists of both acidic gases and aerosols, this paper will focus primarily on acidic aerosols as the gases have received extensive attention. Furthermore, the scope of the discussion will be limited to clinical studies that evaluate effects of the acid aerosols on lung mechanics.

The objective of the clinical study is clear: it is an attempt to establish conditions in a controlled laboratory setting which are relevant to ambient pollutant atmospheres, and to document any health-related effects which result from breathing these atmospheres. Since the lung is the initial target of most inhaled air pollutants, measurements of lung mechanics take on a primary role in toxicologic assessments. Measurements of pulmonary function to assess responses to air pollutants have recently been reviewed (1).

The limitations of clinical studies have also been previously discussed but it is pertinent to consider them here together with their strengths. These studies, for practical and ethical reasons, must be limited to small groups presumably representative of larger populations, to short durations of exposure, and to pollutant concentrations that are expected to produce only mild and totally reversible responses. In addition, laboratory atmospheres are typically simple rather than the com-

plex mixtures, for example, that constitute ambient acid precipitation.

Despite these limitations, however, carefully controlled experimental studies have produced several advances in our understanding of acute effects of exposure to critical air pollutants. First, the importance of exercise in potentiating responses to inhaled pollutants at ambient levels has been established. For example, until recently inhalation of ozone concentrations higher than 0.3 ppm had been considered necessary to induce airway effects. However, when combined with heavy intermittent exercise, exposure to ozone levels as low as 0.12 ppm have caused symptoms and spirometric changes in normal subjects (2).

Secondly, clinical studies have successfully defended the concept of "sensitive" or "susceptible" subgroups. Here again, until recently, exposures to sulfur dioxide (SO_2) in concentrations found in ambient air failed to provoke responses. It is now clear that asthmatic subjects exposed to SO_2 levels as low as 0.25 ppm, when performing isocapnic hyperventilation or during exercise-induced ventilation, can manifest symptomatic and objective evidence of bronchoconstriction (3). Indeed asthmatics may be an order of magnitude more sensitive to SO_2 than nonsensitive healthy adults. The following discussion will conclude that similar differences in sensitivity to sulfuric acid aerosols have now been established between normal and asthmatic individuals.

Human Studies of Sulfate and Sulfuric Acid Effects

In the atmosphere, the major acid sulfate species include ammonium sulfate ($(\text{NH}_4)_2\text{SO}_4$), ammonium bis-

*Department of Medicine and Radiation Biology and Biology and Biophysics, University of Rochester School of Medicine, Rochester, NY 14642

ulfate (NH_4HSO_4), and sulfuric acid (H_2SO_4). In the laboratory, pulmonary responses of normal and asthmatic subjects have been assessed following exposure to each of these acids.

Inhalation Studies with Normal Subjects

It has now been over 30 years since Amdur and colleagues (4) first reported exposure data of healthy volunteers to sulfuric acid mists. To date, the only consensus finding is the absence of pulmonary function effects at sulfate concentrations of less than $100 \mu\text{g}/\text{m}^3$ even after exposures of several hours of and intermittent exercise.

Effects on pulmonary function at higher levels of exposure have been less consistent. In two of the initial studies, brief exposures to sulfuric acid mists at concentrations of $300\text{--}5000 \mu\text{g}/\text{m}^3$ for 5–15 min (4) or $3,000\text{--}39,000 \mu\text{g}/\text{m}^3$ for 10–60 min (5) provoked changes in respiratory pattern, cough, and bronchoconstriction. Even at the lowest exposure level of $350 \mu\text{g}/\text{m}^3$ during quiet ventilation, Amdur et al. (4) observed a 20% decrease in maximum expiratory and inspiratory flow rates and a 35% increase in respiratory rates.

Horvath and co-workers (6) examined 11 normal subjects in an environmental chamber breathing concentrations of H_2SO_4 ranging from approximately 200 to $950 \mu\text{g}/\text{m}^3$ with mass median aerodynamic diameter (MMAD) = $0.9 \mu\text{m}$ for 2 hr. During the exposure, 20-min cycles of rest and exercise (minute ventilation of $\sim 30 \text{ L}/\text{min}$) were alternated. At the high level ($950 \mu\text{g}/\text{m}^3$), cough and throat irritation were frequently noted, and forced 1-sec expiratory volume (FEV_1) decreased marginally but significantly (average = 101 mL) post-exposure; no pulmonary changes occurred at lower H_2SO_4 concentrations. Covert et al. (7) observed mild small airway constriction to result with intermittent exercise and inhalation of $500 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$.

Recently, studies in our laboratory examined normal subjects performing moderate exercise ($300 \text{ kg}\cdot\text{m}/\text{min}$) in environmental chamber atmospheres at $100 \mu\text{g}/\text{m}^3$ and $450 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$ for 4 hr (MMAD = $0.8 \mu\text{m}$) (8). Changes in pulmonary function did not occur either immediately or 24 hr after inhalation. To determine if aerosol exposure caused increased reactivity to a known bronchoconstrictor, all subjects inhaled carbachol following each 4-hr exposure and 24 hr after exposure. At 24 hr after the $450 \mu\text{g}/\text{m}^3$ exposure, 8 of 14 subjects experienced mild throat irritation. At 24 hr post exposure, there was also significant enhancement of the carbachol bronchoconstrictor response after the $450 \mu\text{g}/\text{m}^3$ concentration. These data indicate to us that airway hyperreactivity to H_2SO_4 may occur after a latent period.

In a study using oral inhalation, Utell et al. (9) measured bronchial reactivity in normals after brief exposures to H_2SO_4 , NH_4HSO_4 , $(\text{NH}_4)_2\text{SO}_4$, and sodium bisulfate (NaHSO_4) at concentrations of $1000 \mu\text{g}/\text{m}^3$ (MMAD = $1.1 \mu\text{m}$). Only marginal changes in flow rates were observed after $1000 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$. In contrast, the

bronchoconstrictor action of carbachol was potentiated by the sulfate aerosols more or less in relation to their acidity. Only prior inhalation of H_2SO_4 and NH_4HSO_4 enhanced the carbachol response.

Several human experimental studies have not reported alterations in lung function with exposures to high sulfate concentrations. No decrement in pulmonary function was observed in normal subjects exposed at rest for 10 minutes at concentrations up to $1000 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$ (MMAD = $0.1 \mu\text{m}$) (10) or after 2-hr exposures at $1000 \mu\text{g}/\text{m}^3$ with intermittent light exercise (11).

Inhalation Studies with Asthmatic Subjects

In view of the sensitivity of exercising asthmatics to effects of SO_2 , the responses to inhaled acid sulfate aerosols is of considerable interest. The results of studies with acidic sulfates are summarized in Table 1.

Sackner et al. (10) reported no alteration in lung mechanics in six asthmatics exposed at rest to H_2SO_4 particles (MMAD = $0.1 \mu\text{m}$) at 10, 100, and $1000 \mu\text{g}/\text{m}^3$ for 10 min. Avol and colleagues (12) examined six asthmatics during light exercise (doubled minute ventilation) at $75 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$ (MMAD = $0.3 \mu\text{m}$) for 2 hr in a chamber. Although significant changes in lung function did not occur for the group, two of the six asthmatics "showed possible meaningful changes in resistance."

Two of the most recent clinical studies (13,14) have demonstrated that asthmatic subjects are an order of magnitude more sensitive to H_2SO_4 than healthy, sedentary adults. That is, whereas normal subjects display minimal bronchoconstriction at approximately $1000 \mu\text{g}/\text{m}^3$, asthmatics develop significant changes in airway mechanics at $450 \mu\text{g}/\text{m}^3$ at rest and at $100 \mu\text{g}/\text{m}^3$ during light to moderate exercise.

Koenig et al. (13) exposed 10 adolescents with extrinsic asthma and exercise-induced bronchospasm to $100 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$ during 30 min at rest followed by 10 min of exercise. Mouthpiece inhalation of H_2SO_4 during exercise produced significantly greater alterations in FEV_1 , \dot{V}_{max} 50, and total respiratory resistance than a control NaCl aerosol. The authors reported that the changes in lung function after H_2SO_4 were equivalent to effects induced by sulfur dioxide in a group of adolescent asthmatics (15). In contrast to the experience with gaseous pollutant, it is conceivable that oral route of inhalation of particulate sulfates may, in fact, minimize airway responses due to ammonia neutralization (see below).

In our laboratory, we evaluated the existence of a dose-response relationship to sulfate aerosols including NaHSO_4 , $(\text{NH}_4)_2\text{SO}_4$, NH_4HSO_4 , and H_2SO_4 , with a control NaCl (mean MMAD = $0.8 \mu\text{m}$) in carbachol-sensitive asthmatics (14). Concentrations of $100 \mu\text{g}/\text{m}^3$, $450 \mu\text{g}/\text{m}^3$, and $1000 \mu\text{g}/\text{m}^3$ were inhaled for 16 min via a mouthpiece. At the $1000 \mu\text{g}/\text{m}^3$ concentration, H_2SO_4 and NH_4HSO_4 inhalation produced significant reductions in specific airway conductance and FEV_1 com-

Table 1. Pulmonary effects of sulfuric acid aerosols in asthmatics.

Investigator	Design	Effects
Sackner et al. (10)	Six asthmatics inhaled 10, 100, 1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 for 10 min orally at rest (MMAD = 0.1 μm)	No pulmonary function changes; no alteration in gas exchange
Avol et al. (12)	Six asthmatics inhaled 75 $\mu\text{g}/\text{m}^3$ H_2SO_4 for 2 hr in chamber with exercise (MMAD = 0.3 μm)	Two of 6 subjects showed "possibly meaningful changes in respiratory resistance"
Koenig et al. (13)	Ten adolescent asthmatics with exercise-induced bronchospasm inhaled 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 for 40 min via mouthpiece with exercise (MMAD = 0.6 μm)	Significant reductions in \dot{V}_{max} , FEV_1 , and total respiratory resistance compared to NaCl exposure or pre-exposure
Utell et al. (14)	17 carbachol-sensitive asthmatics inhaled 100, 450, 1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 for 16 min via mouthpiece at rest (MMAD = 1.1 μm)	1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 and NH_4HSO_4 caused significant decline in SG_{aw} and FEV_1 ; 450 $\mu\text{g}/\text{m}^3$ H_2SO_4 produced significant fall in airway conductance; no change after 100 $\mu\text{g}/\text{m}^3$ H_2SO_4
Utell et al. (17)	12 asthmatics inhaled 100, 450 $\mu\text{g}/\text{m}^3$ for 4 hr in chamber with exercise (MMAD = 0.8 μm)	Reduction in FEV_1 and SG_{aw} after one and 2 hr of 450 $\mu\text{g}/\text{m}^3$ inhalation; no change after 100 $\mu\text{g}/\text{m}^3$ H_2SO_4
Spektor et al. (16)	Ten asthmatics inhaled 100, 300, 1000 $\mu\text{g}/\text{m}^3$ for 1 hr via nasal mask at rest (MMAD = 0.5 μm)	1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 caused significant decline in flow rates and airway conductance in 6 of 10 asymptomatic asthmatics which persisted 3 hr after exposure. Four asthmatics showed large variability in response; no effect after 300 or 100 $\mu\text{g}/\text{m}^3$

pared to NaCl or pre-exposure values. At the 450 $\mu\text{g}/\text{m}^3$ concentration, only H_2SO_4 inhalation produced a significant reduction in airway conductance. At 100 $\mu\text{g}/\text{m}^3$, no significant change in airway function occurred after any sulfate exposure. Unfortunately exercise protocols were not incorporated into the 100 $\mu\text{g}/\text{m}^3$ exposure to assess effects of increased ventilation. However, in two asthmatic subjects there was enhancement of the bronchoconstrictor response to carbachol following exposure to 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 —an indication that airways may have been affected even at the lowest H_2SO_4 concentration (9). Indeed Spektor and colleagues (16) confirmed partially these observations in resting asthmatics demonstrating reductions in flow rates and specific airway conductance after inhalation of 1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 for 1 hr via a nasal mask. No changes in lung function occurred after 300 $\mu\text{g}/\text{m}^3$ or 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 .

Recently, Utell and colleagues (17) examined 12 asthmatics to determine if oral-nasal breathing (environmental chamber) influenced airway responses to sulfuric acid aerosols. Subjects inhaled 100 $\mu\text{g}/\text{m}^3$ and 450 $\mu\text{g}/\text{m}^3$ concentrations for 4 hr with intermittent periods of mild exercise. Reductions in flow rates and airway conductance after 1 and 2 hr of 450 $\mu\text{g}/\text{m}^3$ H_2SO_4 occurred to approximately the same degree as during mouthpiece inhalation. No response to 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 was noted. That the route of sulfate inhalation affects airway responses is unclear. However, our inability to demonstrate effects at 100 $\mu\text{g}/\text{m}^3$ sulfuric acid concentrations suggests that all asthmatics may not be alike—that is, young extrinsic asthmatics may comprise a remarkably sensitive subgroup.

Critique

Variability in experimental protocols has been the rule, not the exception, in clinical studies with particles. Among the difficulties which exist in assessing studies of responses to particulate pollution are those related to particle size and therefore site of deposition. The particle size most effective in provoking airway responses is unclear. Aerosols ranging in nominal size from 0.1 μm to 3.0 μm have been generated for clinical studies. No consensus on ideal size exists. Furthermore, the site of deposition will be influenced not only by initial particle size, but also by lung geometry, hygroscopic growth in the airways, mode and pattern of ventilation, and perhaps lung secretions. If alterations in lung mechanics caused by aerosolized sulfates result in part from nonspecific stimulation of upper airway irritant receptors by large particles, very small (0.1 μm) aerosols, even assuming hygroscopic growth, may be insufficient to stimulate them (10).

It is evident that unique host defenses may also influence responses. For example, in 1977, Larson and colleagues (18) hypothesized that airway ammonia (NH_3) could neutralize inhaled acidic sulfates and thereby mitigate airway responses. Respiratory ammonia levels were found to be higher in the mouth than the nose and the rate of sulfuric acid neutralization was inversely related to particle size (19). To examine the hypothesis that oral NH_3 influences responses to sulfuric acid aerosols, Mariglio et al. (20) measured responses to 350 $\mu\text{g}/\text{m}^3$ in exercising asthmatics at both high and low oral NH_3 levels. The high NH_3 levels sig-

nificantly lessened the H_2SO_4 -induced changes in lung function supporting the Larson hypothesis. Theoretically nasal breathing of large particles (1.0–3.0 μm), perhaps in an environmental chamber, could provoke responses which would not result from small particles (0.1 μm) breathed on a mouthpiece because of effective neutralization.

Implicit in the neutralization hypothesis is the likelihood that acidity *per se* is important. Previously, Lippman and Schlesinger (21) reported the relative irritant potency of major ambient sulfates based on clearance rates in the rabbit. The ranking of irritant potency was $\text{H}_2\text{SO}_4 > \text{NH}_4\text{HSO}_4 > (\text{NH}_4)_2\text{SO}_4, \text{Na}_2\text{SO}_4$; this strongly suggests a relation between hydrogen ion (H^+) concentration and the degree of bronchial mucociliary clearance alterations. It is noteworthy that studies in our laboratory support this ranking of irritant potency as related to altering lung function. We observed a relationship between the acidity of the sulfate aerosol, expressed as the pH measured in aqueous solutions at the same molarity (10^{-2} M), namely H_2SO_4 (pH = 1.8), NH_4HSO_4 (pH = 2.2), NaHSO_4 (pH = 2.5), and $(\text{NH}_4)_2\text{SO}_4$ (pH = 4.8), and the degree of induced bronchoconstrictions (14). Inhalation of more acidic sulfates, H_2SO_4 and NH_4HSO_4 , produced the most significant bronchoconstriction. Exposure to the less acidic sulfate aerosols, NaHSO_4 and $(\text{NH}_4)_2\text{SO}_4$, caused no significant change in lung function. Despite this apparent relationship, the role of the hydrogen ion is complex since numerous airway factors may alter the pH of the particle prior to and after deposition.

Additional evidence for an effect of low level sulfuric acid on the airway is available from several sources. Alterations in mucociliary clearance have occurred in normal volunteers after exposure to 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 for one hour. Leikauf and colleagues (22) observed a diphasic dose-response relationship in that tracheo-bronchial clearance was significantly increased after exposure to 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 , unchanged at 300 $\mu\text{g}/\text{m}^3$, and depressed after 1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 . Thus low level sulfuric acid inhalation with resting ventilation may induce airway irritation without alterations in mechanics. Ultimately such injury could impede airway defenses. Furthermore, Schlesinger (23) presented preliminary evidence that a 1-hr exposure of rabbits to 1000 $\mu\text{g}/\text{m}^3$ H_2SO_4 produced a response at the cellular level. Elevated numbers of neutrophils persisted in lavaged lung fluid and the sulfuric acid exposure altered the performance of *in vitro* phagocytosis. Reduction in *in vitro* adherence and attachment was also observed for macrophages lavaged at various times from the exposed rabbits. In all likelihood, either brief or low level sulfuric acid may influence host defenses.

With the impressive array of changes in lung function described by Koenig (13) after 100 $\mu\text{g}/\text{m}^3$ H_2SO_4 in exercising asthmatics, it seems surprising that no alterations in lung mechanics have been observed at even lower levels. For instance, why is it that sensitive asthmatics have not been noted to respond at 50 $\mu\text{g}/\text{m}^3$ H_2SO_4 ? The answer is intriguing albeit simple, namely,

no studies have addressed responses at these low sulfuric acid concentrations. What is needed is a series of studies similar to those performed with SO_2 , that is, low-level H_2SO_4 exposures with heavy, intense exercise in young, allergic (extrinsic) asthmatics. Equally perplexing is the complete void of understanding of acid sulfate effects on individuals at the extreme end of the clinical spectrum, those with chronic obstructive pulmonary disease (COPD). In this perhaps a most sensitive group, currently no data exist.

Nitrogen Dioxide (NO_2)

Currently the effects of NO_2 inhalation are under intensive investigation. Until recently, controlled NO_2 exposures have not produced changes in pulmonary mechanics at concentrations within the ambient range or even higher (24). With the emergence of more experimental studies, evidence has accumulated that asthmatics do indeed bronchoconstrict with inhalation of NO_2 at near ambient levels. In our laboratory, Bauer et al. (25) observed that a 30 min exposure to 0.3 ppm NO_2 produced bronchoconstriction in exercising asthmatics compared to that found with exercising in clean air. Studies with 0.3 ppm NO_2 are presently being repeated at the Environmental Protection Agency and a preliminary report indicates that findings of Bauer et al. in exercising asthmatics have been confirmed (26). In addition, Bauer observed that the NO_2 response was potentiated with cold air inhalation challenge after pulmonary function had returned to baseline. Previous studies had demonstrated increased bronchial reactivity following NO_2 exposure at a level as low as 0.1 ppm (27) or 0.2 ppm (28) but no other studies have produced conflicting findings (29).

In a summary paper in this symposium, Lippmann (30) speculated that the NO_2 effect may be in part an acid effect. He reasoned that since the magnitude of the pulmonary function changes was similar to that experienced by subjects inhaling ozone at 0.2 ppm, and since NO_2 is a much weaker oxidant than ozone, it was conceivable that the NO_2 response was only in part related to the oxidant effect. When NO_2 is absorbed on airway surfaces, it hydrolyzes and releases H^+ ions. Thus, its mechanisms may be similar to that of H_2SO_4 .

Research Needs

Many important questions remain to be addressed: (1) Do young extrinsic (allergic) asthmatics represent a uniquely susceptible subpopulation? The data support a special sensitivity for this group, especially with exposure to acidic aerosols. It is appropriate to examine separately intrinsic and extrinsic (allergic) asthmatics and evaluate the responses of these two groups to intensive exercise at ambient particulate levels. (2) Do individuals with chronic obstructive lung disease (emphysema and chronic bronchitis) deserve inclusion as a sensitive group? Presently too few data exist to address this query. (3) Do exposures to mixtures of acidic aer-

osols and oxidants cause additive effects? To date, combinations of pollutants which comprise acid precipitation have yet to be studied. One recent report concluded that combinations of pollutants (peroxyacetyl nitrate and ozone) produce an interactive effect (31). (4) Can we begin to evaluate mechanisms of H_2SO_4 toxicity in humans by means other than pulmonary mechanics? The answer is a resounding yes. For example, the tool of bronchoalveolar lavage has now been extended to human studies to investigate changes at the cellular level. The evolving relationship between pollutant-induced airway reactivity and increased lavaged human neutrophils (32) and the observations by Schlesinger that brief inhalation of sulfuric acid effect cellular functions in the rabbit, provide background for initiating lavage studies in humans after sulfuric acid exposures.

Obviously, a great deal remains to be learned in the area of human exposures to acidic aerosols.

Conclusions

Based on clinical exposure studies, we now appreciate that the criteria pollutants ozone and sulfur dioxide provoke changes in lung mechanics at high urban concentrations. Although critical gaps still exist in our knowledge of human exposures to acid aerosols, recent data indicate that asthmatics are clearly more sensitive than healthy volunteers and that exercise potentiates responses to sulfuric acid pollutants. Additional studies at even lower sulfate levels combined with intensive exercise and/or other relevant pollutants are required before the gaps can be effectively closed.

The author greatly appreciates the helpful review and discussions with Dr. Paul E. Morrow. Partial support from the National Institute of Environmental Health Science Grant No. ESO2679, a contract from the Health Effects Institute 83-9, a previous contract from the Biomedical Science Department of the General Motors Technical Center, and Division of Research Grant No. RR00044 from the National Institute of Health are acknowledged.

REFERENCES

- Utell, M. J. Measurements of central and peripheral pulmonary function to assess responses to air pollutants: an overview. In: *Inhalation Toxicology of Air Pollution: Clinical Considerations for Regulatory Policy*. (R. Frank, J. J. O'Neill, M. J. Utell, J. D. Hackney, J. Van Ryzin, and P. E. Brubaker, Eds.), American Society for Testing and Materials, Philadelphia, in press.
- McDonnell, W. F., Horstman, D. H., Hazucha, M. J., Seal, E., Salaam, S., and House, D. E. Pulmonary effects of ozone exposure during exercise: dose-response characteristics. *J. Appl. Physiol. Respirat. Environ. Exercise Physiol.* 54: 1345-1352 (1983).
- Sheppard, D., Saisho, A., Nadel, J. A., and Boushey, H. A. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Am. Rev. Respir. Dis.* 123: 486-491 (1981).
- Amdur, M. O., Silverman, L., and Drinker, P. Inhalation of sulfuric acid mist by human subjects. *Arch. Ind. Hyg. Occup. Med.* 6: 305-313 (1952).
- Sims, V. M., and Pattle, R. E. Effects of possible smog irritants on human subjects. *J. Am. Med. Assoc.* 165: 1908-1913 (1957).
- Horvath, S., Folinsbee, L. F., and Bedi, J. F. Effect of large (0.9 μm) sulfuric acid aerosols on human pulmonary function. *Environ. Res.* 28: 123-130 (1982).
- Covert, D., Morgan, M., Larson, T., Frank, N., Horike, M., and Holub, D. Interaction of acid sulfates and the respiratory system. U. S. Environmental Protection Agency, Research Triangle, NC, 1981, EPA Publ. No. (EPA) 600/SI-81-036.
- Utell, M. J., Morrow, P. E., and Hyde, R. W. Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. *J. Aerosol Sci.* 14: 202-205 (1983).
- Utell, M. J., Morrow, P. E., and Hyde, R. W. Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects. *J. Air Pollution Control Assoc.* 34: 931-935 (1984).
- Sackner, M. A., Ford, D., Fernandez, R., Ciplej, J., Perez, D., Kwoka, M., Reinhart, M., Michaelson, E. D., Schreck, R., and Wanner, A. Effects of sulfuric acid aerosol on cardiopulmonary function in dogs, sheep, and humans. *Am. Rev. Respir. Dis.* 118: 497-510 (1978).
- Newhouse, M. T., Dolovich, M., Obminsk, G., and Wolff, R. K. Effects of TLV levels of SO_2 and H_2SO_4 on bronchial clearance in exercising man. *Arch. Environ. Health* 19: 38-50 (1978).
- Avol, E. L., Jones, M. P., Bailey, R. M., Chang, N. N., Kleinman, M. T., Linn, W. S., Bell, K. A., and Hackney, J. D. Controlled exposures of human volunteers to sulfate aerosols. *Am. Rev. Respir. Dis.* 120: 319-326 (1979).
- Koenig, J. Q., Pierson, W. E., and Horike, M. The effect of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. *Am. Rev. Respir. Dis.* 128: 221-225 (1983).
- Utell, M. J., Morrow, P. E., Speers, D. M., Darling, J., and Hyde, R. W. Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. *Am. Rev. Respir. Dis.* 128: 444-450 (1983).
- Koenig, J. Q., Pierson, W. E., Horike, M., and Frank, R. A comparison of the pulmonary effects of 0.5 ppm versus 1.0 ppm sulfur dioxide plus sodium chloride droplet in asthmatic adolescents. *J. Toxicol. Environ. Health* 11: 129-139 (1983).
- Spektor, D. M., Leikauf, G. D., Albert, R. E., and Lippmann, M. Effects of submicrometer sulfuric acid aerosols on mucociliary transport and respiratory mechanics in asymptomatic asthmatics. *Environ. Res.* 37: 174-191 (1985).
- Utell, M. J., Morrow, P. E., Mariglio, J. A., Bauer, M. A., Speers, D. M., Gibb, F. R., and Hyde, R. W. Exercise, age, and route of inhalation influence airway responses to sulfuric acid aerosols in exercising asthmatics (abstract). *Am. Rev. Respir. Dis.* 129: A175 (1984).
- Larson, T. V., Covert, D. S., Frank, R., and Charlson, R. J. Ammonia in the human airways: neutralization of inspired acid sulfate aerosols. *Science* 197: 161-163 (1977).
- Larson, T. V., Frank, R., Covert, D. S., Holub, D., and Morgan, M. S. Measurements of respiratory ammonia and the chemical neutralization of inhaled sulfuric acid aerosol in anesthetized dogs. *Am. Rev. Respir. Dis.* 125: 502-506 (1982).
- Mariglio, J. A., Utell, M. J., Morrow, P. E., Speers, D. M., Gibb, F. R., and Platner, J. Endogenous oral ammonia inhibits sulfuric acid aerosol induced bronchoconstriction in exercising asthmatics (abstract). *Am. Rev. Respir. Dis.* 127: 161 (1983).
- Lippmann, M., and Schlesinger, R. B. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. *J. Toxicol. Environ. Health* 13: 261-289 (1984).
- Leikauf, G., Yeates, D. B., Wales, K. A., Spektor, D., Albert, R. E., and Lippmann, M. Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. *Am. Ind. Hyg. Assoc. J.* 42: 273-282 (1981).
- Schlesinger, R. B. Effects of inhaled acids on respiratory tract defense systems. *Environ. Health Perspect.* 63: 25-38 (1985).
- Hackney, J. D., Thiede, F. C., Linn, W. S., Pederson, E. E., Spier, C. E., Law, D. C., and Fischer, D. A. Experimental studies on human health effects of air pollutants. IV. Short-term physiological and clinical effects of nitrogen dioxide exposure. *Arch. Environ. Health* 33: 176-181 (1978).
- Bauer, M. A., Utell, M. J., Morrow, P. E., Speers, D. M., and Gibb, F. R. 0.30 ppm nitrogen dioxide inhalation potentiates exercise-induced bronchoconstriction in asthmatics (abstract). *Am. Rev. Respir. Dis.* 129: A151 (1984).
- Roger, L. J., Horstman, D. H., McDonnell, W. F., Kehrl, H., Seal, E., Chapman, R. S., and Massaro, E. J. Pulmonary effects in asthmatics exposed to 0.3 ppm NO_2 during repeated exercise

- (abstract). *Toxicologist* 5: 70 (1985).
27. Orehek, J., Massari, J. P., Gayrard, P., Grimaud, C., and Charpin, J. Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. *J. Clin. Invest.* 57: 301-307 (1976).
 28. Kleinman, M. T., Bailey, R. M., Linn, W. S., Anderson, K. R., Whynot, J. D., Shamoo, D. A., and Hackney, J. D. Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. *J. Toxicol. Environ. Health* 12: 815-826 (1983).
 29. Hazucha, M. J., Ginsberg, J. F., McDonnell, W. F., Haak, E. D., Jr., Pimmel, R. L., Salaam, S. A., House, D. E., and Bromberg, P. A. Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 54: 730-739 (1983).
 30. Lippmann, M. Airborne acidity: estimates of exposure and human health effects. *Environ. Health Perspect.* 63: 63-70 (1985).
 31. Drechsler-Parks, D. M., Bedi, J. F., and Horvath, S. M. Interaction of peroxyacetyl nitrate and ozone on pulmonary functions. *Am. Rev. Respir. Dis.* 130: 1033-1037 (1984).
 32. Seltzer, J., Geffroy, B., Stulbarg, M., Holtzman, M. J., Nadel, J. A., and Boushey, H. A., Jr. Association between airway inflammation and changes in bronchial reactivity induced by ozone exposure in human subjects (abstract). *Am. Rev. Respir. Dis.*